Asymmetric Synthesis of 5-Substituted γ-Lactones and Butenolides via Nucleophilic Additions to Oxycarbenium Ions Derived from 5(R)-(Menthyloxy)-4(R)-(phenylsulfanyl)-2(3H)-dihydrofuranone

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Optically active 5-alkyl-substituted butenolides and γ-lactones are attractive building blocks in natural product synthesis[1] and comprise structural moieties frequently present in, e.g., insect pheromones,[2] cardenolides,[3] lignans, and flavor components.[4] Efficient and stereoselective synthetic routes to these products in enantiomerically pure form are highly desirable.[5] As part of our explorative studies toward the use of 5(*R*)-(menthyloxy)-2(5*H*)-furanone (**1**) as a chiral synthon,[6,7] the enantioselective synthesis of a number of naturally occurring lignans has been reported.[8]

5(*R*)-(Menthyloxy)-2(5*H*)-furanone (**1**) reacts with thiophenol and a catalytic amount of triethylamine to give stereospecifically and in excellent yield the trans addition product **2** (Scheme 1), which features an attractive functional group arrangement to generate α-sulfanyl oxycarbenium ion **3**. Here we report the fast and highly stereoselective transformations of **2** to 5-alkyl-substituted 4-(phenylsulfanyl)-2(3*H*)-dihydrofuranones **4** or 4-(menthyloxy)-3-(phenylsulfanyl) carboxylic acids **5**, which are precursors for butenolides and γ-lactones.

Various methods for C−C bond formation via Lewis acid-mediated reactions of acetals with nucleophiles have been developed.[9] As demonstrated by a number of groups,[10] there is a mechanistic divergence between S_N2- and S_N1-type processes. It has been shown that Lewis acid-mediated additions of silylated nucleophiles to α- and β-sulfanyl-substituted aldehydes proceed with excellent diastereoselectivities.[11] Furthermore, reactions of α-sulfanyl acetals with carbon nucleophiles have been studied by Saigo and co-workers.[12] In furanone **2**, an α-sulfanyl-substituted, mixed acyloxy−alkoxy acetal moiety is present, and upon treatment with a Lewis acid it is observed that the acyloxy acetal bond is always broken[13] and this reaction path leaves only two likely intermediates (Figure 1). The stereoselectivity of these reactions can be rationalized by the Felkin−Ahn model, and conformers **A** and **B** lead to anti and syn adducts, respectively. Conformer **A** is preferred, and in most cases the anti adduct is the only detectable diastereomer.

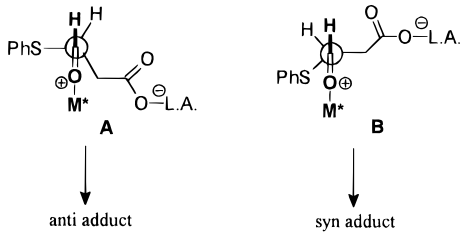
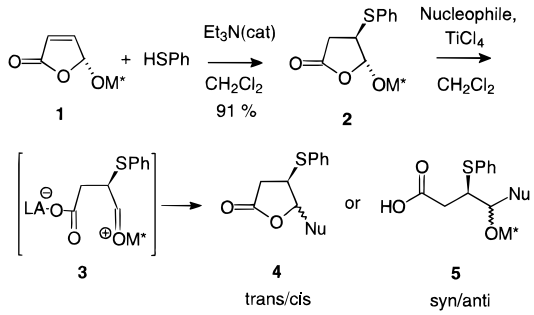


Figure 1.

Scheme 1



When 4(*R*)-(phenylsulfanyl)-substituted furanone **2** is treated at −70 °C with 1−2 equiv of $TiCl_4$ in the presence of a variety of nucleophiles such as allylsilanes, silyl enol ethers, or diorganozinc reagents a very fast reaction occurs. After a reaction time of 5 min and subsequent aqueous workup, β,γ-substituted acids **5** are isolated in 56−72% yield and in most cases with a diastereomeric ratio >98:2 according to ^1H and ^{13}C NMR (Scheme 2, path A, Table 1, entries 2, 4, 6, 8, and 12). In addition to the acids **5** small amounts of lactones **4** (5−20%) are also found in the crude product, but these could be easily separated.

When the addition of nucleophiles **9**−**16** is performed in the presence of 2 equiv of $TiCl_4$ for 1 min at ambient temperature, followed by aqueous workup, the lactones **4** are obtained. In a few cases small amounts of the acids **5** (≤10%) are also formed. Apparently, the intermediate **6** is activated by the excess of Lewis acid present, and upon addition of water hydrolysis to the hydroxy acid **8**

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Scheme 2

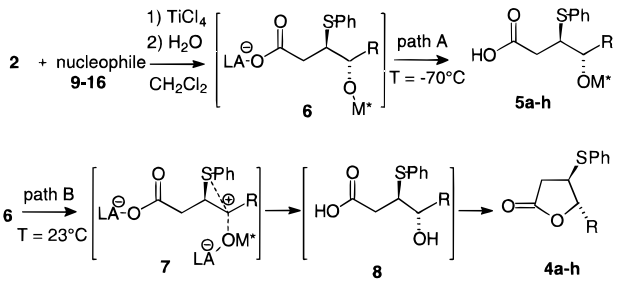
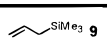
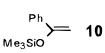
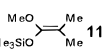
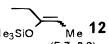
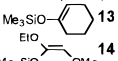
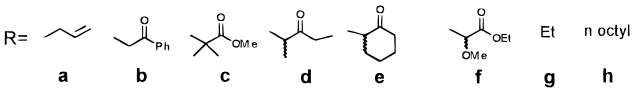


Table 1. Additions of Nucleophiles to Oxycarbenium Ions Derived from 2

Entry	Nucleophile	T (°C)	time (min)	Product (R)	(ratio [a])	Yield [b] %	trans : cis [c] (anti : syn [c])
1	 **9**	23	1	**4a/5a**	(>9 : 1)	50	92 :8
2		-70	5	**5a/4a**	(8 : 2)	56	9 :1
3	 **10**	23	1	**4b/5b**	(>9 : 1)	65	>98 :2
4		-70	5	**5b/4b**	(8 : 2)	59	>98 :2
5	 **11**	23	1	**4c/5c**	(>9 : 1)	66	>98 :2
6		-70	5	**5c/4c**	(9 : 1)	72	>98 :2
7	 **12** (E:Z 8:2)	23	1	**4d/5d**	(>9 : 1)	74	>98 :2[d]
8		-70	5	**5d/4d**	(8 : 2)	52	>98 :2[d]
9	 **13**	23	1	**4e/5e**	(>9 : 1)	57	>98 :2[d]
10	**14**	23	1	**4f/5f**	(>9 : 1)	74	53 : 47[d]
11		23	2	**4g/5g**	(>9 : 1)	56	9 :1
12	Et_2Zn **15**	-70	5	**5g/4g**	(9 : 1)	57	>98 :2
13	$(octyl)_2Zn$ **16**	23	5	**4h/5h**	(>9 : 1)	53	>98 :2

[a]Ratio determined by ^1H NMR. [b]Isolated yield of the major isomer. [c]Ratio determined by ^1H and ^{13}C NMR of the crude product. [d] Diastereomeric ratio of the exocyclic stereogenic center was in the order of 6 : 4 in all four cases (entry 7-10).

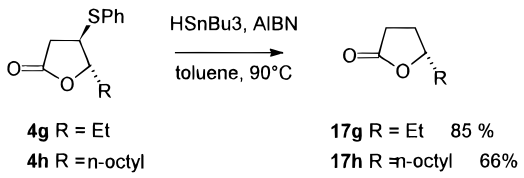


followed by lactonization takes place (Scheme 2, path B). A key feature of the second Lewis acid-mediated step is the stereoselective cleavage of the auxiliary group assisted by the α-sulfanyl functionality. Except for **4f**, trans lactones **4** are formed as the major, or in most cases only detectable, diastereomer. Even in the few cases (entries 1 and 11, Table 1) where small amounts of cis lactones **4** were obtained, these could be separated by simple column chromatography using silica gel.

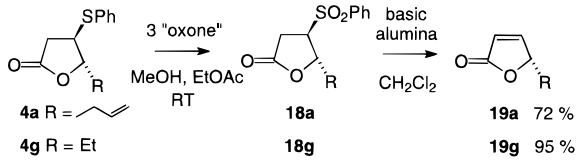
Single crystal X-ray analysis of **4b** confirmed the trans relationship of the substituents at C_4 and C_5.[21] The trans configuration for the products **4a**−**e**,**g**,**h** has been assigned by comparison on the basis of ^1H NMR coupling constants and on the expected mechanistic similarity in this reaction for all nucleophiles used.[14]

The enantiomerically pure 5(*S*)-alkyl-4(*R*)-(phenylsulfanyl)-2(3*H*)-dihydrofuranones **4** are excellent precursors for 5-alkyl-substituted butenolides or butanolides,[15,16] whereas the phenylsulfanyl substituent allows a number

Scheme 3



Scheme 4



of synthetically useful transformations. Reductive desulfurization of **4** could best be performed with Bu_3SnH/AIBN and provided enantiomerically pure 5(*S*)-alkyl-2(3*H*)-dihydrofuranones **17** (Scheme 3). The flavor components and insect pheromones[4] 5(*S*)-ethyl-2(3*H*)-dihydrofuranone (**17g**) [85% yield, $[\alpha]_D = -50$ (*c* 1, MeOH) (lit.[17] $[\alpha]_D = -53.2$ (*c* 1, MeOH))] and 5(*S*)-octyl-2(3*H*)-dihydrofuranone (**17h**) [66% yield, $[\alpha]_D = -35$ (*c* 0.48, MeOH) (lit.[17] $[\alpha]_D = -36.8$ (*c* 0.3, MeOH))] were obtained using this procedure.

Alternatively, 5(*S*)-alkyl-2(5*H*)-furanones **19** are accessible via the sulfones **18** (Scheme 4). Oxidation of **4** with Oxone[18] and subsequent elimination with basic alumina in CH_2Cl_2 gave the corresponding 5(*S*)-alkyl-2(5*H*)-furanones **19** in good yields.[19] For example, 5(*S*)-ethyl-2(5*H*)-furanone (**19g**) [95% overall yield, $[\alpha]_D = +105$ (*c* 4.1,CH_2Cl_2) (lit.[20] for 5(*R*)-**19g** $[\alpha]_D = -97.6$ (*c* 2.08, CH_2Cl_2))] and 5(*S*)-(1-prop-2-enyl)-2(5*H*)-furanone (**19a**) (72% overall yield, $[\alpha]_D = +105$ (*c* 1.08, MeOH) were obtained using this procedure.

In conclusion, we have demonstrated that **2** is a valuable synthon for the synthesis of 3,4-disubstituted carboxylic acids, 5-substituted butenolides, and γ-lactones in enantiomerically pure form.

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Supporting Information Available: Experimental procedures for the Lewis acid mediated additions and spectroscopic data for compounds **4a**−**h** and **5a**,**b**,**c**,**d**,**g**. (5 pages).

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(21) The author has deposited atomic coordinates for **4b** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.